IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

FOSSEL

Filing Date: 17 SEP 97

Serial No.: 08/932,227

Title: TOPICAL DELIVERY OF L-ARGININE TO CAUSE BENEFICIAL EFFECTS

Examiner: MULLIS, J.

Group Art Unit: 1711

Att'y Docket: FOS-104-C1

DECLARATION UNDER RULE 132

I, ERIC T. FOSSEL, do hereby declare and say that:

My home address is 909 W. Roxbury Parkway, Chestnut Hill, MA 02467.

I have a PhD degree in Chemistry from Harvard University. The focus of my studies was on biophysical and physical organic chemistry.

I was employed by Harvard Medical School for 25 years from 1970 through 1995, where I was a professor. When I left Harvard Medical School I held the position of Director of Research and Professor. In that capacity, I was responsible for a variety of research projects.

I , ERIC T. FOSSEL, do hereby disclose that I am the true and sole inventor of said patent application no. 08/932,227. I have a duty to assign my invention to New England Property Holdings LLC, PO Box 395, Newton Center, MA 02459.

I have reviewed U.S. Patent Application 08/932,227 entitled Topical Delivery of L-arginine to Cause Beneficial Effects. I have intimate knowledge of the entire specification to include closely analyzing the claims and the drawings. I am totally

familiar with the language of the claims and conversant with the scope thereof. I completely understand the invention as claimed.

I have reviewed United States Patent no. 5,629,002 to Weuffen et al. that was brought to my attention in connection with a rejection for the above noted application. I have thoroughly reviewed the cited art with specific attention drawn toward Example 10 cited by the Examiner, the combination of sodium thiocyanate with short-chain as well as higher molecular weight peptides or proteins in the form of human hair hydrolzyate and with amino acids, the concentration of 4.9 g/liter (28mMoles) of L-arginine in combination with 30 mmoles of sodium, 18 mmoles of potassium, 5 mmoles of magnesium, and 28 mmoles of chloride fails to provide both a sufficient concentration of both L-arginine and lacks the required salts to be therapeutically effective and create an effective hostile biophysical environment that is a requirement.

The 4.9 g/liter in combination with the other ingredients gives a concentration of only 28 mMoles. Specifically when tested the absorption of L-arginine was ineffective when a concentration less than 250mMoles was tested. Furthermore a minimum concentration of ionic salt is required to produce a hostile biophysical environment. The minimum level to create a hostile biophysical environment is 500mMoles, with higher concentrations being more effective. The Weuffen et al. patent fails to teach or disclose the required concentration of L-arginine and ionic salt to be therapeutically effective as shown in the attached results.

I have reviewed United States patent no. 5,595,753 to Hetchman, entitled "Topical Formulations and Methods for Treating Hemorrhoidal Pain and Sphincter and Smooth Muscle Spasm in the Gastrointestinal Tract". The topical preparation disclosed

applies 0.01 to 10 mg of L-arginine per one ml solution, using various delivery vehicles to the sphincter and smooth muscle of the gastrointestinal tract. The mucous membrane of the gastrointestinal tract differs significantly from that of the epidermis in its ability to absorb L-arginine. The Hetchman patent discloses L-arginine in combination with an electrolyte solution. The electrolyte solution has a ionic concentration of 120 mMoles, which while effective for the mucous membrane it is insufficient to produce the hostile biophysical environment necessary to introduce the L-arginine through the epidermal boundary.

As indicated tests conclude that a concentration of 0.1 to 10 mg of L-arginine topically applied to the epidermis is ineffective to produce beneficial results. Further when the cited concentration of L-arginine disclosed is combined with an electrolyte solution, which has an ionic salt concentration of 120 mMoles it is ineffective to produce the hostile biophysical environment.

There has been a long felt need to introduce NO or NO like substances to the epidermis to provide beneficial effects from increased localized blood flow. The use of directly releasing NO substances have large shortcomings such as a very short half life, and detrimental effects because NO is known to bind to hemoglobin and high does of NO are known to be toxic.

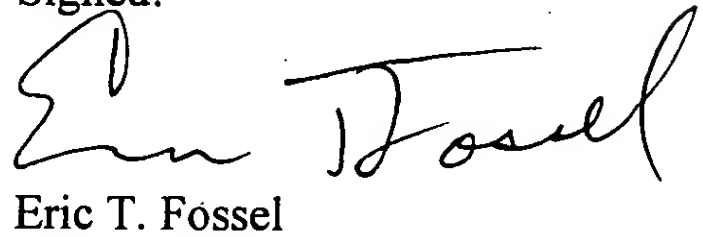
Prior to the instant application the solution to was to provide components that release NO to the skin and ignore the harmful side effects. L-arginine was applied only in internal applications because of the complications of trying to pass the epidermal barrier to provide an effective dosage. The instant application overcame these deficiencies, which caused others to exclude L-arginine for direct application to the

epidermis through the application of L-arginine within a hostile biophysical environment directly to the epidermis.

Further L-arginine overcomes the deficiencies involved with known prior art NO releasing substances by providing a natural precursor to NO production by the body, in addition to the blocking of competitive compounds which block the action of NO production.

All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 8 of the United States Code, and that such willful false statement may jeopardize the validity of the application or any patents issuing thereon.

Signed:



Eric T. Fossel

Date: December 6, 2001